PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K A2

(11) International Publication Number: WO 99/59523 (15 A1)

(43) International Publication Date: 25 November 1999 (25.11.99)

(21) International Application Number: PCT/EP99/03289

(22) International Filing Date: 12 May 1999 (12.05.99)

(30) Priority Data:
MI98A001073 15 May 1998 (15.05.98) IT

(71) Applicant *(for all designated States except US)*: CODEX V S.R.L. [IT/IT]; Circ.ne A. Gramsci, 26, I-04010 Cori (IT).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: DE GREGORIO, Chiara [IT/IT]; Circ.ne Gramsci, 26, I-04010 Cori (IT).

(74) Agent: MINOJA, Fabrizio; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I-20122 Milano (IT).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: TOPICAL PHARMACEUTICAL COMPOSITIONS USEFUL FOR THE TREATMENT OF CUTANEOUS OR CIRCULATORY PATHOLOGIES ON INFLAMMATORY, IMMUNE, PROLIFERATIVE OR DEGENERATIVE BASIS

(57) Abstract

Topical pharmaceutical compositions, containing as active ingredient a mixture of pollen extracts and vegetable oil unsaponifiables, useful for the treatment of cutaneous or circulatory pathologies on inflammatory, immune, proliferative or degenerative basis.

Pg 5 & 15-20 Claims 1 & 3
Pg 8, & 18
Pg text
Pg 15 missing

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

TOPICAL PHARMACEUTICAL COMPOSITIONS USEFUL FOR THE TREATMENT OF CUTANEOUS OR CIRCULATORY PATHOLOGIES ON INFLAMMATORY, IMMUNE, PROLIFERATIVE OR DEGENERATIVE BASIS

The present invention relates to pharmaceutical topical compositions containing pollen extracts and unsaponifiable fractions of vegetable oils for the treatment of cutaneous or circulatory pathologies on inflammatory, immune, proliferative or degenerative basis.

One of the problems of all cutaneous chronic inflammatory pathologies, when the etiological agent causing the inflammatory process itself cannot be removed, is the control of the inflammatory process and the reactivation of the tissue trophism. Chronic inflammatory processes are generally associated with severe dystrophism of the affected tissue, which is mainly related to the impairment of the efficiency of the tissue microcircle (permanent dilation of capillaries and venules with alterations of capillary permeability). When the inflammatory event is on an immunopathogenic basis, said process becomes chronic mainly as a consequence of a persistent alteration of the mutual regulation of the various components of the immune system and/or of cytochemical signals. On the other hand, each inflammatory process on immunopathogenic basis is expected to have a determined duration and naturally end when the exogenous noxae or the "non-self" elements which have triggered the immune process have been eliminated and the involved lymphocytes have undergone apoptosis death.

When the cause which has triggered the disease cannot be removed, the following therapeutical objectives should be attained :

1) control of the chronic inflammatory reaction by modulating self-regulation unbalances of the immune system, also through pharmacological stimulation of any poorly active immunocompetent cells;

2) direct reactivation of tissue trophism by acting on microcircle and on non-immunocompetent cells directly responsible for functionality and well-being of the tissue itself, which are generally involved in the damages related to the inflammatory reaction.

Said objectives are fundamental in case of both cutaneous and systemic, inflammatory pathologies. Therefore, a medicament exerting the above mentioned action on cutaneous pathologies could also be used in the case of systemic pathologies by means of a suitably formulated transdermal system. At present the available medicaments comprise steroidal or nonsteroidal, topical or systemic, immunosuppressors. On the other hand, the long-term topical and systemic side-effects of corticosteroids on tissue trophism are well known. Immunosuppressors such as cyclosporin have in their turn precise limits of use. Very few nonsteroidal anti-inflammatory drugs are useful to some extent in cutaneous chronic inflammatory pathologies, in that they are poorly active and induce pharmacological tolerance to the antiinflammatory action, even after short times. According to the available knowledge, wide-spectrum immunomodulators are known to induce no pharmacological

tolerance to the antiinflammatory effect, while exerting a direct reactivation of cutaneous trophism, nor substances exerting a strong trophic effect in physiological conditions as well as an immunomodulating effect in pathological conditions, thanks to their vasoactive and vasogenic actions.

It has now unexpectedly been found that the combination of pollen extracts with vegetable oil unsaponifiables, administered topically, provides advantageous therapeutical results which are surprisingly resolutive in the treatment of the skin pathologies. This means that the topical formulations comprising said combination not only have a lenitive or symptomatic pharmacological activity, but also can cause, in a high number of cases, the even complete remission of the pathology, without relapses after the treatment has been interrupted.

The pollen extract is a complex mixture of natural substances and nutrients which has been used in the cosmetic art, thanks to its emollient and restitutive properties, in combination with other active principles having similar or complementary activity. Pollen extract is commercially available (see, for example, G. Proserpio, A. Malpede, A.M. Massera, Fitocosmetopea Sinerga, Sinerga Ed. 1995; CTFA Buyer's Guide) and it essentially comprises a mixture of protides (10-35%), glucides (15-40%), lipids (1-10%), salts, oligoelements, vitamins and a water content from 10 to 20%. It further contains a series of C_{27}, C_{26} and C_{29}-sterols, as reported in Phytochemistry, 1968, Vol. 7, 1361-1365.

Pollen extract also has a series of further applications, generally related to the well-being of the

body and of course depending on the type of extraction process as well as on the purity degree or concentration obtained.

In fact, being a natural nutrient, it is added to foodstuff intended for the improvement of psychophysical conditions in humans. For example, CN 1100599 describes a concentrate of pollen extracts for fighting *fatigue and mental uneasiness*. Similarly, KR 9400320, SU 1660668, EP 87669 disclose the alimentary use of pollen extracts in combination with other nutrients.

One widespread use of pollen extract is anyway in the cosmetic field, as active component with adjuvating action, generally in formulation with other active principles, excipients and carriers known in the art and useful for the intended purpose. Thus, for example, US 4737360 discloses *skin care compositions comprising a pollen extract and a blend of natural oils as carriers to increase skin permeability*. Also JP 52090635, JP 6287106, RU 2054926, SU 1806736, SU 1785684, SU 1734751, SU 1713555, SU 1683750, SU 1597192, FR 2631824, FR 2597337, SU 992057 disclose formulations for the cosmetic use, mainly as face-creams, in which pollen extracts are mixed with a series of skin protective or nutritive components.

Pollen extracts are also used in the preparation of *toilets soaps* (SU 1691390, SU 1618759), *tooth-pastes* (SU 1007671), *lipsticks* (SU 1486167), *hair-care compositions* (RU 2072831, SU 997681).

It has also been described, albeit not very often, a potential use of pollen extract as a complement or supplement of pharmacological treatments in various allergic (EP 201053, JP 5076597), tumor (EP 220453, US

5744187), infective (RU 2090198), inflammatory (FR 2142194, RO 80826, JP 9278665, CN 8603867) pathologies, as well as in other pharmaceutical applications (CH 381358, EP 499015, US 3906092).

Conversely, no specific pharmacological properties or activities are known, ascribable to the unsaponifiable fraction obtainable from vegetable oils, such as olive, soybean, wheat germ, sunflower, avocado, sesame, almond, safflower, carrot seeds, peanut, hazelnut, castor oils and the like. Said oils are used per se in the alimentary field, as well as carriers, excipients, binders in topical cosmetic or pharmaceutical formulations, such as oils, gel, creams, pastes and the like.

The unsaponifiable fractions of said vegetable oils are a minimum percentage (0.5 to 3.5%) and substantially consist of mixtures of carotenoids, branched hydrocarbons, flavonoids, phytosterols and other products having a complex, still partially unknown structure.

Likewise, no combinations of pollen extracts with significant amounts of vegetable oil unsaponifiables, preferably of olive, soybean and wheat germ oils, are known, having pharmacological properties, in particular therapeutical activity on cutaneous or circulatory pathologies of various origin.

It has now unexpectedly been found that formulations comprising as active ingredient a combination of pollen extracts and vegetable oil unsaponifiables, optionally in combination with other active principles with adjuvating, complementary or supplementing activity, exert a potent, often resolutive

therapeutical action in many different affections of the skin.

The formulations of the present invention, in particular those for the topical use, can unexpectedly modulate the vascularization of dermal tissues.

"Modulation of the vascularization" means the ability to restore the activity and efficiency of microcircle, when it has been impaired by conditions causing either its excessive (in chronic inflammatory conditions, psoriasis, etc.), or its insufficient (in senescence, dermal atrophy, etc.) development, with consequent hypervascularization or insufficient vascularization.

In fact, the formulations of the invention proved to be active both in limiting and controlling the hypervascularization characteristic of chronic inflammatory conditions, and in activating microcircle when it is inefficient or reduced due to various causes.

The effect on microcircle is therefore due to this balancing activity. The experimental results have, in fact, evidenced that, independently of the cause of microcircle inefficiency (such as chronic inflammatory conditions, alteration of large venous vessels, venous insufficiency in lower limbs, tissue dystrophy or atrophy due to hormonal insufficiency, senescence, and the like), the formulations of the invention prevent degeneration of microcircle functionality, restoring its natural equilibrium (modulating action).

It has also unexpectedly been found that the modulating action on microvessels is combined with a wide-spectrum immunomodulation action on all immuno pathogenic mechanisms. Said effect resolves the

inflammatory component, whether it is the cause of microcircle impairment or a parallel event.

Furthermore, the formulations of the invention, thanks to their modulating action on microcircle, show a high penetration into the deep layers of the skin, acting as a particularly effective transdermal system, attaining therefore the non-symptomatic resolution of chronic pathologies. For example, complete resolution of psoriasic plaques has been obtained, in cases of vulgaris chronic psoriasis localized in limited, rapid-absorption areas. Observation after one-month treatment evidenced the disappearance of the lesion and the onset of repigmentation of the area from the edges to the centre. After two-month treatment neither signs of the preceding lesion nor dyschromic areas were observed. The skin had an healthy, repigmentated appearance and the capillaroscopic pattern was similar to that of healthy skin. The treatment was carried out for a further month, thus equilibrating the concerned area and avoiding relapses.

As a consequence of the features described above, the topical compositions of the invention also exert a strong trophic action on the skin, as they have high moisturizing power, keratoplastic effect due to keratinization equilibrating activity and peripheral sebomodulating action.

The formulations of the invention are also useful in the treatment of skin ageing, microtelangiectasias and couperose, dystrophic skin (also as a consequence of pharmacological treatments, for example with corticosteroids). Furthermore, they are also useful in the moisturizing and sebomodulating treatment of acne

and seborrheic conditions, in that they act through a peripheral mechanism not involving the systemic transit. They also exert a moderate peripheral antiinflammatory action together with a trophic and moisturizing effect on the skin, contrary to the known antiinflammatories.

The formulations of the invention are also very effective in the antiage treatment of the skin, in that they exert a real action on skin ageing, acting on all the affected parameters (such as vascularization, which decreases in time), and not only the adjuvant, antilipoperoxidative or moisturizing actions typical of cosmetic compositions. These formulations increase skin microcircle vascularization, therefore significantly improving trophism as well as superficial and deep hydration, while arresting radicalic lipoperoxidation. The obtained results also depend on the duration of the treatment, also as for long-term effects.

According to the invention, the pollen extract is mixed with one or more unsaponifiable fractions of vegetable oils, preferably selected from those obtained from olive, soy-bean or wheat germ oils.

The pollen extract : vegetable oil unsaponifiables weight ratio is not critical, but it usually ranges from 10:1 to 1:10, preferably about 1:1.

The mixture of pollen extract and vegetable oil unsaponifiables is formulated according to the invention preferably in suitable topical administration forms using conventional excipients. Examples of said formulations comprise creams, ointments, lotions, gels, oils, gel-oils, ointments, gauzes or medicated patches and the like. The mixture of pollen extract and vegetable oil unsaponifiables, although per se having a

very good transdermal penetration, can optionally be formulated in a matrix suitable for the transdermal administration.

The compositions of the invention can optionally contain further active principles with adjuvating, complementary or supplementing activities or anyway useful for the therapeutical use. Thus they will contain, for example, zinc oxide, salicylates, collagene, heparinoids and the like.

Isodecyl-ortho-hydroxy-benzoate (isodecylsalicylate) and zinc oxide are particularly preferred.

The weight percentage of the mixture of pollen extract and unsaponifiables is not critical and can range within wide limits, in line with the chemical-physical characteristics of the pharmaceutical formulation. Generally speaking, said percentage will be preferably above 6%, more preferably from 6 to 25% about.

Non limiting examples of cutaneous pathologies on inflammatory, proliferative, immune or degenerative basis which can be treated by means of the topical compositions of the invention comprise chronic dermatitis (atopic, radiodermitis, dyshidrosis, lichenified eczema, allergic and seborrheic dermatitis, etc.); psoriasis and similar parakeratosic conditions; capillaritis, venulitis, vasculitis in general and angiodermitis; Bateman dermatitis; pyodermitis; rosacea; viral pathologies (such as herpes labialis, herpes zoster and Papilloma virus warts; stasis, elderly and obese dermatitis, post-peeling dermatitis, decubitus erythema; telangiectasias.

The compositions of the invention are also useful

in the treatment of skin or circulation pathologies characterized by cell hyperproliferation, such as actinic dyskeratosis and epitheliomas, and exert strong systemic effects in the treatment of chronic venous insufficiency of lower limbs, thanks to their wide-spectrum immunomodulating, vasoactive and vasokinetic characteristics, which induce rapid cicatrization of venous ulcers, reduction in stasis eczema and lymphedema and inhibition of formation of dyschromic events related to these pathologies.

Furthermore, the combinations of the invention are useful in the treatment of pathologies such as arteritis, which require transdermal administration.

Particularly advantageous effects are obtained in irritative dermatitis, dyshidrosis, seborrheic dermatitis, radiodermatitis following radiotherapy in tumor post-surgery, rosacea, capillaritis, venulitis and angiodermitis.

Beneficial effects are also observed in the treatment of actinic dyskeratosis lesions following surgery. Interestingly, patients treated with the formulations of the invention showed no relapses. Treatment of epitheliomas induced very good cicatrization of the lesions, so that no disruptive surgery such as amputations and the like was needed.

Spots from treatments with sclerosing agents, as well as nipple fissures, anus fissures, hemorrhoids, neo-formed pink stretch marks, can also be treated with very good results.

The compositions of the invention can be administered for prolonged times, usually from a few weeks to some months, once or more times a day, prefera-

bly at least twice a day.

The following examples further illustrate in detail the invention.

Example 1

Pollen extract	5%
Wheat germ oil unsaponifiables	2%
Olive oil unsaponifiables	2%
Soybean oil unsaponifiables	1%
Linolenate	3%
Isodecylsalicylate	12%
Carriers for formulating a cream, gel, paste,	q.s. to 100%.

Example 2

Pollen extract	5%
Wheat germ, olive and soy-bean unsaponifiables	5%
Zinc oxide	10%
Carriers	q.s. to 100%

Example 3

Pollen extract	5%
Wheat germ, olive and soy-bean unsaponifiables	3%
in lipogel carrier	

Example 4

The therapeutical effectiveness of the preparations of the Examples 1 and 2 in the treatment of atopic dermatitis and irritative dermatitis of hands, resistant to any other treatment, was evaluated. A similar evaluation was carried out on patients affected with telangiectasias.

Tests were performed on 28 patients of both sexes, respectively with:

atopic dermatitis	No. 10 patients
irritative dermatitis of hands	No. 9 patients
telangiectasias	No. 9 patients

Inclusion criteria: both sexes, age 35-65 years, absence of pathologies requiring therapies interfering in the evaluation of the results.

Exclusion criteria: pregnancy, breast feeding, use of contraceptives or steroidal antiinflammatories, patients with diabetes, endocrine, hepatic or renal diseases.

Each patient was kept under observation from the beginning of the protocol until the maximum therapeutical result which could be reached according to the dermatologist. At the end of the protocol, patients were observed for a time during which self-medication was carried out discontinuously. Weekly controls were performed during the whole observation period. Improvement was evaluated according to a 5 semi quantitative score (-1 = worsening; +3 = maximum improvement reachable) and subjected to Friedman's test.

Treatment

Atopic dermatitis

4 Pediatric patients (3-7 years) and 6 adult patients (21-28 years), one of which under treatment with cyclosporin, were treated. The formulation of Example 2 was used in the morning and that of Example 1 at night, every day for 15 days, then 3 times a week during long-term therapy. The patient treated with Cyclosporin was treated with the formulation of Example 2 in the morning and that of Example 1 at night for long-term therapy.

Irritative dermatitis of hands

9 Female patients (28-43 years) with chronic irritative dermatitis of hands resistant to usual treatments. Tests carried out before the study excluded contact allergic dermatitis. Patients were treated with the formulation of Example 1 in the morning and that of Example 2 at night, every day for one month, then three times a week during long-term therapy. 4 Female patients were used as controls, which were treated with a common moisturizing cream.

Telangiectasias

9 Female patients (11-67 years), suffering from face dermatosis of various severity (couperose, persistent erythrosis, rosacea, rhinophyma). Patients were treated in the morning and at night with the formulations of Examples 1 and 2 for three months. Capillaroscopic evaluation on the right and left zygomatic areas was carried out at 30 x with Macroblitz probe (CIR) and Sony microcamera, using Dermavision software, at the beginning and at the end of the treatment.

Results

Atopic dermatitis

At the end of the first 15-day treatment, all patients showed a marked improvement of both erythematous and xerosic lesions. 8 patients out of 10 showed an improvement higher than 70% and the remaining 2 an improvement higher than 40%. The cyclosporin patient showed a marked improvement of the lesions with reduction in all erythematous lesions and disappearance of the xerotic ones.

Irritative dermatitis of hands

At the end of the one-month treatment, all patients showed a marked improvement: 6 patients an improvement higher than 70%, and 3 from 40% to 70%. Even after 4-month intermittent therapy, results proved satisfactory. When treatment was interrupted, symptoms reappeared in a short time. 3 Patients out of 4 treated with the common moisturizing cream showed at the end of the treatment a poor improvement, lower than 40%, and 1 showed no improvement.

Telangiectasias

At the end of the treatment, the complete resolution of the disease was attained in five patients and a marked improvement in the remaining four.

Example 5

The therapeutical efficacy of the formulation of Example 3 in the treatment of face warts. A female patient (21 years) with flat warts as well as filiform warts diffused on the face was treated twice a day with the formulation of Example 3.

After one-month treatment, observation evidenced the remarkable reduction of the filiform warts and the almost complete disappearance of flat warts.

The same treatment on a further 5 cases gave satisfactory results as well.

capillaritis, venulitis, vasculitis, angiodermitis, dermoipodermiti, rosacea, herpes labialis, herpes zoster, actinic dyskeratosis, epitheliomas, telangiectasias.

CLAIMS

1. Topical pharmaceutical compositions containing as active ingredient a mixture of pollen extracts and vegetable oil unsaponifiables.

2. Compositions as claimed in claim 1, in which the vegetable oil unsaponifiables are selected from olive oil, soybean oil and wheat germ oil unsaponifiables.

3. Compositions as claimed in claim 1 or 2, in the form of creams, ointments, lotions, gel, oils, gel-oils, ointments, gauzes or medicated patches.

4. Compositions according to any one of the above claims, further comprising other active principles with adjuvating, complementary or supplementing activity, selected from zinc oxide, salicylates, collagene, heparinoids.

5. Compositions as claimed in claim 4, comprising as complementary active ingredient isodecyl-ortho-hydroxy-benzoate.

6. Compositions as claimed in claim 4, comprising as complementary active ingredient zinc oxide.

7. Compositions according to any one of the above claims in formulations suitable for the transdermal administration.

8. The use of a mixture of pollen extracts and vegetable oil unsaponifiables for the preparation of topical or transdermal medicaments having modulating activity on skin vascularization, for the treatment of cutaneous or circulatory pathologies on inflammatory, immune, proliferative or degenerative basis.

9. The use as claimed in claim 8 in which the pathologies are chronic dermatitis, psoriasis,

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 45/06, 7/48

A3

(11) International Publication Number: **WO 99/59523**
(15) A3

(43) International Publication Date: 25 November 1999 (25.11.99)

(21) International Application Number: PCT/EP99/03289

(22) International Filing Date: 12 May 1999 (12.05.99)

(30) Priority Data:
MI98A001073 15 May 1998 (15.05.98) IT

(71) Applicant *(for all designated States except US)*: CODEX V S.R.L. [IT/IT]; Circ.ne A. Gramsci, 26, I-04010 Cori (IT).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: DE GREGORIO, Chiara [IT/IT]; Circ.ne Gramsci, 26, I-04010 Cori (IT).

(74) Agent: MINOJA, Fabrizio; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I-20122 Milano (IT).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
29 December 1999 (29.12.99)

(54) Title: TOPICAL PHARMACEUTICAL COMPOSITIONS USEFUL FOR THE TREATMENT OF CUTANEOUS OR CIRCULATORY PATHOLOGIES ON INFLAMMATORY, IMMUNE, PROLIFERATIVE OR DEGENERATIVE BASIS

(57) Abstract

Topical pharmaceutical compositions, containing as active ingredient a mixture of pollen extracts and vegetable oil unsaponifiables, useful for the treatment of cutaneous or circulatory pathologies on inflammatory, immune, proliferative or degenerative basis.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/03289

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K45/06 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 0 858 799 A (UNILEVER PLC) 19 August 1998 (1998-08-19) page 12	1-3,7

X	G. RIALDI: "Assessment of the Biological Activity on Filagrinn by a Natural Derivative for Skin Care Applications" IN-COSMETICS CONFERENCE, vol. IV, March 1993 (1993-03), pages 45-52, XP002119893 page 45 page 47 page 48	1-3,7-9

X	EP 0 279 136 A (CLARINS) 24 August 1988 (1988-08-24)	1-4,6-8
Y	column 2, line 18-31; claims 1,6,7,9; example	1,7-9

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 October 1999	18/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kanbier, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/03289

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 332 501 A (PAYOT N G LAB) 13 September 1989 (1989-09-13) column 12, line 10-15; example 12	1-3,7
X A	FR 2 324 293 A (ORLANE) 15 April 1977 (1977-04-15) page 1, line 1-5; example 4 page 2, line 13-17; claims 3,4	1,3,4,7, 8 2
X	FRANCE WORLD CONTACTS, 'Online! 1996, XP002119894 Retrieved from the Internet: <URL:www.francecontacts.com/marche/Beaute0 ceane/bo10.htm> 'retrieved on 1999-10-14! the whole document	1,7,8
X	EP 0 521 647 A (UNILEVER PLC) 7 January 1993 (1993-01-07) example 1	1-3,7
Y	FR 2 142 194 A (SOCIBRE) 26 January 1973 (1973-01-26) cited in the application page 3, line 18-27	1,7-9
A	WO 98 05294 A (HYLDGAARD J) 12 February 1998 (1998-02-12) page 1, paragraph 1 page 1, line 3-6 page 1, line 28,29 page 18, line 20-22 page 18, line 26-28 page 24, line 15-25 page 24, line 27-31 page 26, line 23,24: claim 1	1,4,6-8
A	PARENT ET AL: "Spreading of psoriatic plaques: alteration of epidermal differentiation" JOURNAL OF INVESTIGATIVE DERMATOLOGY, vol. 95, no. 3, September 1990 (1990-09), pages 333-340, XP002119895 the whole document	1,8,9
A	WO 98 06714 A (HENKEL CORP) 19 February 1998 (1998-02-19) page 1, line 23 -page 2, line 6 page 6, line 14 -page 7, line 2 page 8, line 15-17; claims 16-19	1,2
A	CH 381 358 A (GABER) cited in the application claim 1	1,3

-/--

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/03289

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 499 015 A (FOCKERMAN) 19 August 1992 (1992-08-19) cited in the application	1

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/03289

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0858799 A	19-08-1998	AU 5386598 A	20-08-1998
		CA 2229271 A	14-08-1998
		CN 1196237 A	21-10-1998
		JP 10226634 A	25-08-1998
		NZ 329701 A	30-08-1999
		US 5855893 A	05-01-1999
EP 0279136 A	24-08-1988	FR 2597337 A	23-10-1987
EP 0332501 A	13-09-1989	FR 2628005 A	08-09-1989
		AT 105506 T	15-05-1994
		DE 68915191 D	16-06-1994
		DE 68915191 T	25-08-1994
		ES 2052038 T	01-07-1994
FR 2324293 A	15-04-1977	BE 841216 A	28-10-1976
		DE 2617919 A	11-11-1976
		ES 447476 A	16-07-1978
		JP 51139636 A	02-12-1976
EP 0521647 A	07-01-1993	US 5118507 A	02-06-1992
		AT 130753 T	15-12-1995
		AU 652837 B	08-09-1994
		AU 1850692 A	07-01-1993
		CA 2072027 A,C	26-12-1992
		DE 69206336 D	11-01-1996
		DE 69206336 T	25-04-1996
		ES 2081054 T	16-02-1996
		JP 2042664 C	09-04-1996
		JP 5186327 A	27-07-1993
		JP 7064717 B	12-07-1995
		NZ 243253 A	25-02-1994
		ZA 9204712 A	27-12-1993
FR 2142194 A	26-01-1973	NONE	
WO 9805294 A	12-02-1998	AU 3692097 A	25-02-1998
		EP 0915693 A	19-05-1999
WO 9806714 A	19-02-1998	US 5686632 A	11-11-1997
		AU 3912297 A	06-03-1998
		EP 0925293 A	30-06-1999
CH 381358 A		NONE	
EP 0499015 A	19-08-1992	AT 148341 T	15-02-1997
		AU 668348 B	02-05-1996
		AU 1277992 A	15-09-1992
		CA 2104114 A	16-08-1992
		DE 69217206 D	13-03-1997
		DE 69217206 T	28-08-1997
		DK 571491 T	11-08-1997
		EP 0571491 A	01-12-1993
		EP 0707851 A	24-04-1996
		ES 2100335 T	16-06-1997
		JP 6508103 T	14-09-1994
		NZ 241633 A	27-06-1994
		WO 9214458 A	03-09-1992

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/EP 99/03289

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-9
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/03289

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0499015 A		US 5449794 A	12-09-1995